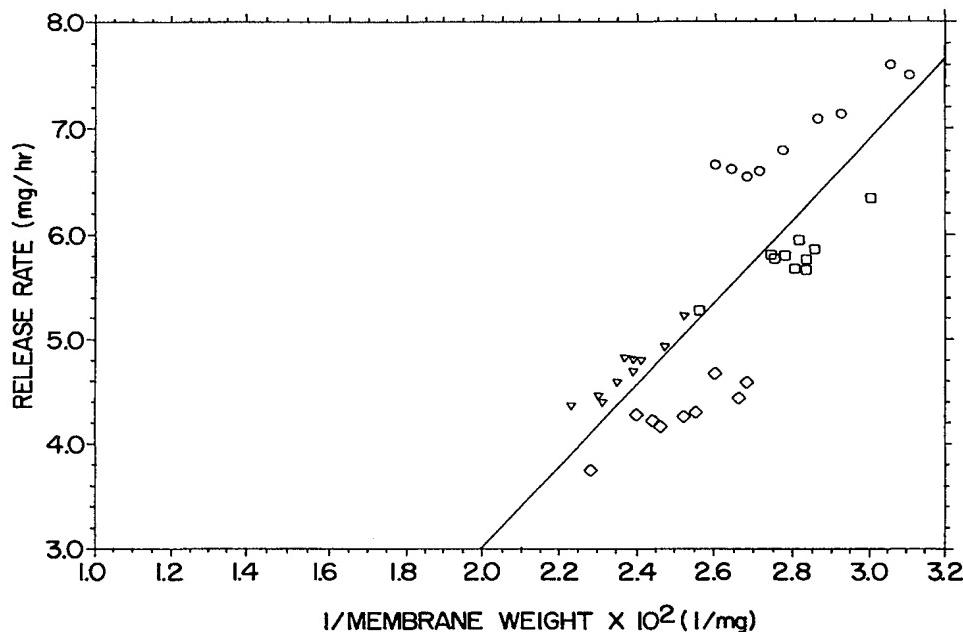




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(54) Title: PHARMACEUTICAL COATING COMPOSITION AND METHOD OF USE



(57) Abstract

A composition comprising a polymer for providing a polymer membrane, at least one pharmaceutically acceptable surfactant compatible with the polymer, and a single solvent for both the polymer and the surfactant. The composition is particularly apt for coating pharmaceutical dosage forms.

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1        **PHARMACEUTICAL COATING COMPOSITION AND METHOD OF USE**

2

3        **FIELD OF THE INVENTION**

4

5            This invention pertains to a novel and useful pharmaceutical coating  
6 composition. More particularly, the invention related to a pharmaceutically  
7 acceptable composition comprising at least one polymer and at least one  
8 surfactant which composition with a single solvent can be coated onto a  
9 dosage form. The invention concerns also a process of coating a dosage  
10 form with the composition and the solvent.

11

12

13        **BACKGROUND OF THE INVENTION**

14

15            In Remington's Pharmaceutical Sciences, 14th, Ed., p 1681, published  
16 in 1970, it was reported that pill coating has been a pharmaceutical technique  
17 for well over ten centuries. For example, Rhazes (850-932 A.D.) used  
18 mucilage, a seaweed substance, for coating pills in the ninth century, and  
19 Avicenna (980-1037 A.D.) is credited with the introduction of silver and gold  
20 pill coatings into medicine. The coating of pills with finely powdered talcum,  
21 called pearl coating, was popular in previous times. Gelatin coating of pills  
22 was introduced into medicine by Garot in 1838. The first sugar-coated pills in  
23 the United States were imported from France in about 1842. The first sugar-  
24 coated pill was manufactured in the United States in 1856 by Warner, a  
25 Philadelphia pharmacist. In about 1884 Unna introduced enteric coated pills.

26

27            Unique pharmaceutically-acceptable tablets, manufactured as an  
28 osmotic dosage form entered the fields of medicine and pharmacy with the  
29 invention of osmotic dosage forms by inventors Theeuwes and Higuchi in  
30 U. S. Patent Nos. 3,845,770 and 3,916,899. The osmotic dosage forms  
disclosed in these patents comprise a semipermeable membrane that

1 surrounds a compartment containing a therapeutic agent. The membrane is  
2 permeable to the passage of an external fluid, and it is impermeable to the  
3 passage of drug. There is at least one exit through the membrane for  
4 delivering the therapeutic agent from the osmotic dosage form.

5 A pioneering advancement in osmotic dosage forms was made  
6 available to the drug dispensing arts in U. S. Patent No. 4,327,725 by  
7 patentees Cortese and Theeuwes. The invention provided by these inventors  
8 concerned an osmotic dosage form for delivering a therapeutic agent, that  
9 because of its solubility, is difficult to deliver in therapeutic amounts at a  
10 controlled rate over time. The dosage form of U. S. Patent No. 4,327,725  
11 comprises a semipermeable wall that surrounds a therapeutic agent and an  
12 expandable agent. In operation, the expandable agent in the presence of  
13 imbibed fluid, expands and pushes the therapeutic agent through an exit  
14 passageway from the dosage form.

15 While the above presented dosage forms are useful for the  
16 management of health and disease, a serious disadvantage is associated  
17 with their manufacture. That is, the prior art used two or more solvents to  
18 dissolve a coating-forming membrane and a flux enhancer, because one  
19 solvent does not dissolve both the membrane and the flux enhancer. A  
20 typical solvent system used by the prior art for this purpose comprises two or  
21 more organic solvents, often possessing degrees of unknown incompatibility.  
22 Further, the prior art solvents often produced high-flux membranes that  
23 exhibited mechanical defects, which lead to weakened membranes  
24 accompanied by brittleness. Then too, the use of multiple solvent can  
25 produce haziness or opacity in a membrane, which makes it impossible to  
26 identify selected regions of a dosage form. Also, the use of multiple organic  
27 solvents presents an environmental problem as the solvents require  
28 complicated recover systems to avoid contaminating the environment, which  
29 recovery systems are expensive to install and to operate.

1           It will be appreciated by those skilled in the drug dispensing art, that if  
2       a coating is provided that comprises a single solvent and its substantively-free  
3       of excessive organic solvent for coating dosage forms, such a coating and its  
4       accompanying solvent would have an immediate positive value, and  
5       concomitantly, represent an advancement in the drug coat and drug coating  
6       art. Likewise, it will be appreciated by those versed in the coat and process-  
7       coating arts, that if a coat and a process for coating are made available for  
8       dosage forms that overcome the disadvantages known to the prior art, they  
9       would have a practical application in the fields of medicine and pharmacy.

10

11

12           **OBJECTS OF THE INVENTION**

13

14           Accordingly, in view of the above presentation, it is an immediate  
15       object of this invention to provide a novel and useful coating composition for  
16       dosage forms, and which coating composition overcomes the disadvantages  
17       associated with the prior art.

18           Another object of this invention is to provide a new coating composition  
19       comprising pharmaceutically acceptable ingredients, and which coating  
20       composition is innocuous and useful for manufacturing a dosage form.

21           Another object of this invention is to provide a nontoxic coating  
22       composition, which coating composition is useful for making dosage forms.

23           Another object of this invention is to provide a coating composition  
24       comprising a membrane and a surfactant, which coating composition is  
25       capable of being applied to a dosage form without difficulty and is applied at  
26       relative lower cost.

27           Another object of this invention is to provide a composition comprising  
28       a membrane and a surfactant, and a common solvent for the membrane and  
29       the surfactant.

1           Another object of the invention is to provide a coating composition  
2 characterized by simplicity of formulation, ease of manufacture and a single  
3 solvent system that can be used to form a coating solution that avoids binary or  
4 tertiary solvent systems.

5           Other objects, features and advantages of this invention, will be more  
6 apparent to those versed in the dispensing art from the following detailed  
7 specification taken in conjunction with the drawings and the accompanied  
8 claims.

9

10           **BRIEF DESCRIPTION OF THE DRAWINGS**

11

12           In the drawing figures, which are not drawn to scale, but are set forth to  
13 illustrate various embodiments of the invention, the drawing figures are as  
14 follows:

15

16           Drawing Figure 1 depicts the release rate vs the reciprocal membrane  
17 weight for two coating conditions.

18           Drawing Figure 2 depicts the release rate vs the reciprocal membrane  
19 weight sprayed from two ethanol/water ratios.

20           Drawing Figure 3 depicts a membrane surfactant composition coated  
21 from a single solvent from three coating runs.

22           Drawing Figure 4 depicts membranes coated from a binary solvent  
23 from four coating runs.

24           In the drawing figures and in the specification, like parts in related  
25 figures are identified by like numbers. The terms appearing earlier in the  
26 specification and in the description of the drawing figures, as well as in  
27 embodiments thereof, are further described elsewhere in this disclosure.

28

29

30

DETAILED DESCRIPTION OF THE INVENTION

2

3        In accordance with the practice of this invention, a therapeutic agent,  
4 including a drug, is coated with a composition comprising a polymer and a  
5 surfactant. The polymer in the process of coating the therapeutic agent  
6 converts to a membrane that surrounds the therapeutic agent to yield a dosage  
7 form. The polymer is nontoxic, and it does not adversely affect an animal  
8 host, including a human, and a therapeutically-acceptable drug. The  
9 polymers useful for providing a membrane comprise a member selected from  
10 the group consisting of cellulose ester, cellulose ether, and cellulose ester-  
11 ether. Representative of specific polymers comprise a member selected from  
12 the group consisting of cellulose acylate, cellulose diacylate, cellulose  
13 triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate, and  
14 ethylcellulose. The amount of polymer on a weight based in a coating  
15 composition in a final, dry coated membrane is 40 wt % to 99.5 wt %.

16        In coating composition comprising the polymer also comprises one or  
17 more pharmaceutically acceptable surfactants. The surfactant generally for  
18 the purpose of this invention is amphiphilic as it contains both a hydrophobic  
19 and a hydrophilic group. Representative of surfactants that exhibit solubility  
20 in aqueous and nonaqueous solvents are polyoxyethylene fatty acid esters  
21 that includes polyoxyethylene monostearate, polyoxyethylene sorbitan  
22 monopalmitate, polyoxypropylene glycols that include polyoxypropylene  
23 glycol having a molecular weight of 950 and 3 moles to 85 moles of ethylene  
24 oxide, polyoxypropylene glycol possessing a molecular weight of 1200 and 7  
25 to 40 moles of ethylene glycol, polyoxypropylene glycol possessing a mole  
26 weight of 1750 and 5 moles to 160 moles of ethylene oxide, polyoxypropylene  
27 glycol having a molecular weight of 2050 and 10 moles to 110 moles of  
28 ethylene oxide, polyoxypropylene glycol having a 2250 molecular weight and  
29 5 moles to 200 moles of ethylene oxide, polyoxypropylene glycol possessing  
30 a molecular weight of 2750 and 15 to 250 moles of ethylene oxide, and

1 polyoxypropylene glycol of 3250 molecular weight and 8 moles to 300 moles  
2 of ethylene glycol. The amount of surfactant in a composition for coating is  
3 0.5 wt % to 60 wt %.

4 Other pharmaceutically acceptable surfactants for the purpose of this  
5 invention include triblock copolymers of ethylene oxide-propylene oxide,  
6 ethylene oxide, which include polymers with an average molecular weight of  
7 2200 and 3 to 20 moles of ethylene oxide, polymers with molecular weight  
8 8,600 and 50 to 110 moles of ethylene oxide, polymers with molecular weight  
9 of 7800 and 45 to 80 moles of ethylene oxide, polymers with 15,000  
10 molecular weight and 110 to 170 moles of ethylene oxide, and those with  
11 molecular weight 12,200 and 70 to 130 moles of ethylene oxide.

12 Other pharmaceutically acceptable surfactants suitable for use in this  
13 invention include monoglycerides, diglycerides, sorbitan fatty acid esters,  
14 polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol esters,  
15 polyoxyethylene esters of acids, polyoxyethylene alcohols, polyoxyethylene  
16 glyceride ester, polyoxyethylene-oxypropylene monostearate with 10 to 40  
17 moles of ethylene oxide, polyoxyethylene alkyl amine, ionic surfactants such  
18 as N-cetyl-ethyl morpholinium ethosulfate, N-soya-n-ethyl morpholinium  
19 ethosulfate, alkyl aryl sulfonate, polyoxyethylene ether, polyoxyethylene  
20 glyceride alkyl aryl sulfonate blend, polyoxyethylene alkyl aryl ether-alkyl aryl  
21 sulfonate blend, nonionic-anionic blends, and polyethylene sorbitol oleate-  
22 polyoxyethylene amine blend.

23 The composition for providing the coating composition comprises of  
24 0 wt % to 30 wt % of a surfactant polymer of hydroxypropylcellulose of 7,500  
25 to 150,000 weight average molecular weight, and 0 wt % to 30 wt % of a  
26 polyvinylpyrrolidone of 1,200 to 225,000 viscosity average molecular weight.  
27 A coloring agent, a colorant, or opacifying agent can be added to the  
28 composition to identify the dosage form. The colorant should be  
29 pharmaceutically acceptable as represented by FD & C Red No. 3, FD & C  
30 Red No. 40, FD & C Yellow No. 5, FD & C Yellow No. 6, FD & C Blue No. 1,

1 FD & C Blue No. 2, FD & C Green No. 5, and iron oxides including black,  
2 yellow and red iron oxides. The opacifying agent should be pharmaceutically  
3 acceptable such as finely-divided titanium dioxide. The amount of colorant or  
4 opacifying agent in a composition is 0 wt % to 3.5 wt %.

5        Optionally, other functional excipients can be formulated within the  
6 coating composition such as anti-tack agents to improve coating quality and  
7 ease of processing. Anti-tack agents can be incorporated within the coating  
8 single-solvent composition in dissolved form or in the dispersed form. Anti-  
9 tack agents are formulated at zero to five weight percent based on the drug  
10 weight of the coating composition. These agents include glycerol fatty acid  
11 esters such as glycerol monostearate, fats of glycerides of saturated C12 to  
12 C18 fatty acids, esters of medium chain fatty acids such as, coconut oil, palm  
13 kernel oil, babassu oil, finely divided silicon dioxide, silica aluminates, talc,  
14 precipitated silicas, fumed silicas, metal fatty acids such as magnesium  
15 stearate, fatty acids saturated C12 to C18 such as stearic acids, and  
16 saturated C12 to C18 alcohol such as stearyl alcohol.

17        The dosage form, when manufactured as an osmotic dosage form with  
18 controlled-release properties comprises at least one exit in the dosage form  
19 membrane. The phase controlled-release as used herein, indicates that  
20 control is exercised over both the duration and the profile of the drug-release  
21 pattern. The expression passageway, as used for the purpose of this  
22 invention, includes aperture, orifice, bore, pore, porous element through  
23 which the drug can be pumped, diffuse, travel or migrate, a hollow fiber,  
24 capillary tube, porous overlay, porous insert, microporous member, and  
25 porous composition. The expression also includes a compound that erodes  
26 or is leached from the membrane in the fluid environment of use to produce at  
27 least one passageway in dosage form. Representative compounds suitable  
28 for forming at least one passageway, or a multiplicity of passageways,  
29 includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall;  
30 a gelatinous filament; a water-removable poly(vinyl alcohol); leachable

1 compounds such as fluid removable pore-forming polysaccharides, acid,  
2 salts, or oxides. A passageway or a plurality of passageways can be formed  
3 by a leaching a compound such as sorbitol, sucrose, lactose, fructose, or the  
4 like, from the membrane to provide a controlled-release dimensioned pore-  
5 passageway. The passageway can have any shape such as round,  
6 triangular, square, elliptical, and the like, for assisting in the controlled-  
7 metered release of drug from dosage form. Dosage form can be constructed  
8 with one or passageways in spaced apart relation to one or more surfaces of  
9 a dosage form. Passageway and equipment for forming passageways are  
10 disclosed in U.S. Patent Nos. 3,845,770 and 3,916,899 by Theeuwes and  
11 Higuchi; in U.S. Patent No. 4,063,064 by Saunders et al.; and in U.S. Patent  
12 No. 4,088,864 by Theeuwes et al. Passageways comprising controlled  
13 releasing dimension, sized, shaped and adapted as a releasing-pore formed  
14 by aqueous leaching to provide a releasing-pore formed by aqueous leaching  
15 to provide a releasing-pore of controlled release-rate are disclosed in U.S.  
16 Patent No. 4,200,098 by Ayer and Theeuwes; and in U.S. Patent No.  
17 4,285,987 by Ayer and Theeuwes.

18 The membrane is manufactured and applied in one process,  
19 comprises an air suspension process. This procedure consists in suspending  
20 and tumbling a compressed drug core comprising a single layer or a bilayer  
21 core, in a current of air and wall forming composition until a wall is applied to  
22 the core. The air suspension procedure is well-suited for independently  
23 forming the wall. The air suspension procedure is described in U.S. Patent  
24 2,799,241; J. A. Pharm. Assoc., Volume 48, pages 451 to 454, (1959); and  
25 *ibid*, Volume 49, pages 82 to 84, (1960).

26 The dosage form can be coated in an air suspension coat, or by other  
27 membrane forming techniques such as pan-coating systems, wherein  
28 membrane forming compositions are deposited by successive spraying of the  
29 composition on the drug-core compartment, accompanied by tumbling in a  
30 rotating pan. Finally, the membrane coated compartments are dried in a

1 forced air over at 30° C to 50° C for up to a week to free dosage form 10 of  
2 solvent. Generally, the membrane formed by these techniques have a  
3 thickness of 1 to 30 mils (0.254 mm to 0.762 mm, with a presently preferred  
4 thickness of 4 to 10 mils, 0.101 mm to 0.254 mm).

5 The dosage form of the invention is manufactured by standard  
6 manufacturing techniques. For example, in one manufacture the drug and  
7 other core-forming ingredients comprising a single drug layer or bilayer core  
8 facing the exit means are blended and pressed into a solid layer, or a solid  
9 bilayer. The drug and other ingredients can be dry-blended or blended with a  
10 solvent and mixed into a solid or semisolid formed by conventional methods  
11 such as ball-milling, calendaring, stirring, roll-milling or churning and then  
12 pressed into a preselected shape. The layer possesses dimensions that  
13 correspond to the internal dimensions of the area the layer is to occupy in the  
14 dosage form and in a bilayer it also possesses dimensions corresponding to  
15 the second layer for forming a contracting arrangement therewith. Next, in a  
16 bilayer core, the push layer is placed in contact with the drug layer. The push  
17 layer is manufactured using techniques for providing the drug layer. The  
18 layering of the drug layer and the push layer can be fabricated by convention  
19 press-layering techniques. Finally, a single layer or the two layer  
20 compartment, the layer or layers are surrounded with a membrane. A  
21 passageway is laser, leached, or mechanically drilled through the membrane  
22 to contact the drug layer. When the passageway is formed by a laser, the  
23 dosage form is optically-oriented automatically by the laser equipment for  
24 forming the passageway on the preselected surface for forming the  
25 passageway.

26 In another manufacture, the dosage form is manufactured by the wet  
27 granulation technique. In the wet granulation technique, for example, the  
28 drug and the ingredients comprising the drug-forming layer are blended using  
29 a solvent, such as ethyl alcohol-water 98:2 v:v (volume:volume) as the  
30 granulation fluid. Other granulating fluid, such as denatured alcohol 100%,

1 can be used for this purpose. The ingredients forming the drug layer are  
2 individually passed through a 20 mesh screen and then thoroughly blended in  
3 a mixer. Next, other ingredients comprising the drug layer are dissolved in a  
4 portion of the granulation fluid, such as the cosolvent described above. Then,  
5 the latter prepared wet blend is slowly added to the drug blend with continual  
6 mixing in the blender. The granulating fluid is added until a wet blend is  
7 produced, which wet mass than is forced through a 20 mesh screen onto  
8 oven trays. The blend is dried for 18 to 24 hours at 30°C to 50°C. The dry  
9 granules are sized then with a 20 mesh screen. Next, a lubricant is passed  
10 through screen, such as a 80-mesh screen, and added to the dry screen  
11 granule blend. The granulation is placed in a blender and blended for 1 to 15  
12 minutes. A push layer is made by the same wet granulation techniques. The  
13 compositions are pressed into their individual layers in a layer press.

14 Another manufacturing process that can be used for providing the  
15 compartment-forming composition layers comprises blending the powdered  
16 ingredients for each layer independently in a fluid bed granulator. After the  
17 powdered are dry blended in the granulator, a granulating fluid, for example,  
18 poly(vinylpyrrolidone) in water, or in denatured alcohol, is sprayed on the  
19 powders. Optionally, the ingredients can be dissolved or suspended in the  
20 granulating fluid. The coated powders are then dried in a granulator. This  
21 process granulated all the ingredients present therein while added the  
22 granulating fluid. After the granules are dried, a lubricant such as stearic acid  
23 or magnesium stearate is added to the granulator. The granules for each  
24 separate layer are pressed then in the manner described above.

25 The dosage form of the invention can be manufactured by mixing a  
26 drug with composition-forming ingredients and pressing the composition into  
27 a layer possessing dimensions that correspond to the internal dimensions of  
28 the compartment of the dosage form. In another manufacture the drug and  
29 other drug composition-forming ingredients and a solvent are mixed into a  
30 solid, or a semisolid, by conventional methods such as ballmilling, shaking,

1 calendaring, tumbling, stirring or rollmilling, and then pressed into a  
2 preselected layer-forming shape. Next, a layer of a composition comprising  
3 an osmopolymer and an optional osmagent are placed in contact the drug  
4 layer. The layering of the first layer comprising the drug and the second layer  
5 comprising the osmopolymer and optional osmagent composition can be  
6 accomplished by using a conventional layer press technique. The wall can be  
7 applied by molding, brushing, spraying or dipping the pressed bilayer's  
8 shapes with all-forming materials. another and preferred technique that can  
9 be used for applying the wall is the air-suspension coating procedure. This  
10 procedure consists in suspending and tumbling the two contacting layers in  
11 current of air until the wall-forming composition surrounds the layers. The air  
12 suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm.*  
13 *Assoc.*, Vol. 48 pp 451-454 (1979); and, abid, Vol. 49, pp 82-84 (1960).  
14 Other standard manufacturing procedures are described in *Modern Plastics*  
15 *Encyclopedia*, Vol. 46, pp 62-70 (1969); and in *Pharmaceutical Science*, by  
16 Remington, 14th Ed., pp 1626-1678 (1970), published by Mack Publishing  
17 Co., Easton, Pa.

18 Exemplary solvents suitable for manufacturing the wall, a single layer  
19 and a bilayer core include inert inorganic and organic solvents final laminated  
20 wall. The solvents broadly include a single solvent members selected for the  
21 group consisting of aqueous solvent, alcohol, ketone, ester, ether, aliphatic  
22 hydrocarbon, halogenated solvent, cyclaliphatic, aromatic, and heterocyclic  
23 solvents. Typical solvents include acetone, diacetone, alcohol, methanol,  
24 ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate,  
25 isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl  
26 ketone, n-hexane, n-heptane ethylene glycol monoethyl ether, ethylene glycol  
27 monoethyl acetate, methylene dichloride, ethylene dichloride, propylene  
28 dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane,  
29 tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane,  
30 benzene, toluene, naptha, tetrahydrofuran, and diglyme.

1           The expression therapeutically active agent as used for the purposes  
2        of this invention includes a drug, or a composition comprising a  
3        therapeutically active drug and other composition forming ingredients the term  
4        drug includes any physiologically or pharmacologically active substance that  
5        produces a local or a systemic effect in animals including humans. The terms  
6        physiologically and pharmacologically are defined in Stedman's Medical  
7        Dictionary, published by Williams and Wilkins, 1966, Baltimore, MD. The drug  
8        comprise a member selected from the group consisting of anticonvulsant,  
9        analgesic, anti-inflammatory, anesthetic, anti-Parkinson, antimicrobial,  
10      antimalarial, antiviral, antiparasitic, cardiovascular, contraceptive, central  
11      nervous system actant including depressant and stimulant, diuretic,  
12      electrolyte, hormone, hypoglycemic, muscle contractant, muscle relaxant,  
13      hypnotic, ophthalmic, psychic energizer, neoplastic, sedative,  
14      sympathomimetic, and tranquilizer. The drugs are known in Pharmaceutical  
15      Sciences, by Remington, 17th Edition, 1985, published by Mack Publishing  
16      Co., Easton, PA.

17           The drug can be in various pharmaceutically acceptable form, such as  
18      uncharged molecules, molecular complexes, pharmacologically acceptable  
19      salts such as hydrochloride, hydrobromide, sulfate, laurylate, palmitate,  
20      phosphate, nitrate, borate, acetate, maleate, tartrate, oleate and salicylate.  
21      For acidic medicines salts of metals, amines organic cations; for example  
22      quaternary ammonium can be used. Derivatives of medicines, such as an  
23      ester, ether and amides, can be used. Also, a medicine that is water  
24      insoluble can be used in a form that is a water soluble derivative thereof to  
25      serve as a solute, and its release from a dosage form it is converted by  
26      enzymes, hydrolyzed by the body pH, or other metabolic process to the  
27      original biologically active form.

28           Representative of drug that can be administered by this invention  
29      include a member selected from the group consisting of simvastatin  
30      sumatriptan, doxazosin, amlodipine, azithromycin, lisinopril, finasteride,

1 ziprasidone, olanzapine, risperidone, sildenafil, dofetilide, donepezil,  
2 atorvastatin, trovafloxacin, eprosartan, losartan, tasosartan, enalapril,  
3 sertindole, quetiapine, nelfinavir, ritonavir, indinavir, dexlenfluramine, and  
4 citicoline. The dose of drug in a dosage form provided by the invention is  
5 100 micrograms to 1000 milligrams.

6

7

8 **DETAILED DESCRIPTION OF EXAMPLES OF THE INVENTION**

9

10 The following examples are merely illustrative of the present invention  
11 and they should not be considered as limiting the scope of the invention in  
12 any way, as these examples and other equivalents thereof will become more  
13 apparent to those skilled in the drug delivery art in the light of the present  
14 disclosure, the drawings and the accompanying claims.

15

16

**EXAMPLE 1**

17 A series of osmotic therapeutic compositions comprising a dose of  
18 pentoxyfylline were coated with a membrane-forming composition comprising  
19 55 wt % of ethylcellulose having an ethoxyl content of 48.0 to 49.5 weight  
20 percent and a 220,000 molecular weight, 20 wt % of hydroxypropylcellulose  
21 of 60,000 molecular weight, 20 wt % of polyvinylpyrrolidone of 1,300  
22 molecular weight and 5 wt % of polyoxyethylenated stearate comprising 40  
23 moles of ethylene oxide. The wall-forming ingredients were dissolved with  
24 stirring in 100% anhydrous ethanol. Then, the freshly prepared coating  
25 solution was allowed to solvate at room temperature, 20°C, for 72 hours. The  
26 solvated solution was divided into two equal portions. One portion was spray  
27 coated on the therapeutic compositions without stirring the solution, and the  
28 other portion was stirred continuously while the coating was applied to the  
29 therapeutic composition. The performance curves of the resulting dosage  
30 forms were equivalent as seen in Figure 1. Drawing Figure 1 illustrates the

1 release rate vs the reciprocal membrane weight for dosage forms sprayed at  
2 two coating conditions. The clear square indicates membranes formed  
3 unstirred while spraying and the dark squares indicates membranes formed  
4 while spraying the membrane forming composition. The core of the dosage  
5 form comprised a bilayer tablet therapeutic composition. One layer, the drug  
6 layer, weighed 845 mg and consisted of 71 wt % pentoxifylline, 24.67 wt %  
7 polyethylene oxide of 200,000 molecular weight, 4 wt % polyvinylpyrrolidone  
8 of 40,000 molecular weight, 0.25 wt % magnesium stearate and 0.08 wt %  
9 butylated hydroxytoluene. The dosage form comprises a push layer  
10 composition for pushing the therapeutic composition from the dosage form.  
11 The push layer composition weighed 200 mg and consists of 97.70 wt %  
12 polyethylene oxide of 5,000,000 molecular weight, 1 wt %  
13 polyvinylpyrrolidone of 40,000 molecular weight, 1 wt % ferric oxide, 0.25 wt  
14 % magnesium stearate, and 0.05 wt % butylated hydroxyglutuene. The  
15 membrane comprises two round 25 mil (0.635 mm) diameter exits.

16

17 **EXAMPLE 2**

18 A series of therapeutic compositions were prepared for manufacturing  
19 into dosage forms for illustrating the unexpected improvements for the  
20 dosage forms of Example 1 over the dosage forms of Example 2. In Example  
21 2, therapeutic compositions comprising pentoxifylline were coated with a  
22 membrane composition comprising 55 wt % ethylcellulose of 220,000  
23 molecular weight, 22.5 wt % hydroxypropylcellulose of 60,000 molecular  
24 weight and 22.5 wt % of polyethylene glycol of 8,000 molecular weight. The  
25 membrane was coated with a binary solvent system consisting of 3,477 ml of  
26 anhydrous ethanol and 47 ml of water. The membrane coating solution was  
27 prepared by dissolving the ethylcellulose and the hydroxypropylcellulose in  
28 the ethanol and the polyethylene glycol in water and then blending the two  
29 solutions to form the final coating solution. The polyethylene glycol was  
30 soluble in water and in the ethanol binary mixture, but not soluble in ethanol

1 alone. The final coating solution comprised 98.3% ethanol and 1.7% water.  
2 A subsequent coating composition comprised 95% ethanol and 5% water.  
3 The two coating runs produced dosage form comprising membrane of distinct  
4 coating weights. The results of the measured performance of individual  
5 membrane dosage forms for two coating revealed the membranes which  
6 were formed with the coating revealed the membranes which were formed  
7 with the coating solutions having 5% water produced much faster release rate  
8 of drug than membranes of comparable weight coated with 1.7% water as  
9 seen in drawing Figure 2. The wide divergence of these two performance  
10 curves demonstrated that small changes in the ratio of a binary solvent can  
11 produce significantly different permeabilities in membranes. For this binary  
12 system it makes the production of reproducible membrane very different  
13 because it is difficult to keep the ratio of solvents constant from batch to batch  
14 and from within a batch during the coating process.

15 The accompanying drawing Figure 2 illustrates the release rate vs  
16 reciprocal membrane weight for a series of dosage forms comprising  
17 ethylcellulose in the membrane. In the drawing Figure 2, the clear circles  
18 represent a binary solvent comprising 95% ethanol and 5% water and the  
19 clear squares represent a binary solvent system comprising 98.3% ethanol  
20 and 1.7% water. The dosage form of Example 2, comprises a therapeutic  
21 composition weighing 845 mg and consisting of 71% pentoxyfylline, 24.67  
22 wt % polyethylene oxide of 200,000 molecular weight, 4 wt % polyvinyl-  
23 pyrrolidone of 40,000 molecular weight, 0.25 wt % magnesium stearate and  
24 0.08 wt % butylated hydroxytoluene. The dosage form comprises a push  
25 composition in laminated arrangement with the therapeutic composition. The  
26 push composition weigh 200 mg and comprises 97.70 wt % polyethylene  
27 oxide of 5,000,000 molecular weight, 1 wt % polyvinylpyrrolidone of 40,000  
28 molecular weight, 1 wt % ferric oxide, 0.25 wt % magnesium stearate, and  
29 0.05 wt % butylated hydroxytoluene. The release rate form the dosage forms  
30 were measured in artificial gastric juice at 37°C. The dosage form comprised

- 1 two, 25 mil (0.635 mm) exit passageways in the membrane that connected  
2 the therapeutic composition with the exterior of the dosage form.

3

### **EXAMPLE 3**

The procedure of Example 1 is followed in this example. In this example, the therapeutic composition is coated with a membrane composition consisting of 79 wt % cellulose acetate comprising 39.8% acetyl content having molecular weight of 40,000 and 21 wt % of a surfactant comprising 30 wt % polyoxypropylene glycol having a 8,400 molecular weight and 160 moles of ethylene oxide. The coating solution was prepared by dissolving the cellulose acetate and polyoxypropylene glycol in the single solvent with stirring and slight warming to 30°C. The membrane was sprayed from a single solvent consisting of 100% acetone, and the membranes formed from the coating composition was smooth, without cracks or cusps. The uniform morphology for these dosage forms is seen in accompanying drawing Figure 3 showing the performance of the membrane coating. Drawing Figure 3 depicts the results for a drug composition weighing 319 mg consisting of 35 % tacrine hydrochloride, 57 wt % mannitol, 3 wt % hydroxypropylmethylcellulose of 9,200 molecular weight, 1 wt % polyvinylpyrrolidone of 40,000 molecular weight, 3 wt % crosslinked polyvinylpyrrolidone, 1 wt % magnesium stearate which composition is surrounded by the membrane. The dosage form comprises two 10 ml (0.254 mm) exit passageways for releasing the drug from the dosage form. In drawing Figure 3, the clear circles, triangles and squares depict the release pattern for these lots of dosage forms, with each symbol type representing each of three lots. The figure illustrates the data is clustered together, indicating good reproducibility. The morphology of the membranes when observed in cross section under microscopic examination was smooth, without cracks, laminations, striations, or cusps.

29

#### EXAMPLE 4

1            Therapeutic compositions comprising tacrine hydrochloride were  
2    coated with a membrane-forming composition comprising 75 wt % cellulose  
3    acetate comprising a 39.8% acetyl content and having a molecular weight of  
4    40,000, 23 wt % polyvinylpyrrolidone and having a molecular weight of  
5    40,000, and 2 wt % triethylcitrate. The membrane-forming ingredients were  
6    dissolved in a binary solvent comprising 80/20 (wt/wt) acetone/methanol. The  
7    therapeutic compositions were coated with the membrane and the  
8    performance is depicted in drawing Figure 4. In drawing Figure 4, the drug  
9    composition coated with the membrane weighed 321.3 mg, and consisted of  
10   34 wt % tacrine hydrochloride, 60 wt % mannitol, 3 wt %  
11   hydroxypropylmethyl-cellulose of 9, 200 molecular weight, 1 wt %  
12   polyvinylpyrrolidone of 40,000 molecular weight, 1 wt % cross-linked sodium  
13   carboxymethylcellulose, and 1 wt % magnesium stearate. The dosage form  
14   comprises two 10 mil (0.254 mm) exit orifices. In drawing Figure 4, the clear  
15   circles, triangles, squares and diamonds illustrate different dosage forms  
16   release rate analyzed with 10 dosage forms in each of four lots. Each type of  
17   symbol represents one lot. Figure 4 depicts the dosage forms prepared by  
18   using the binary solvent exhibited unacceptable performance as the  
19   reproducibility was poor. The morphology of the membranes under  
20   microscopic examination evidence ranged from homogenous to very  
21   heterogenous. The heterogenous structures were characterized as being  
22   laminar, with striations, cracks, and cusps within the membrane structure.  
23

24                          EXAMPLE 5

25            In this example, ten surfactant flux enhancers were evaluated by  
26    coating 70/30 cellulose acetate/enhancer blends from 100% acetone. The  
27    permeability values of the surfactant enhancer are summarized in Table 1.  
28    The Pluronic F68 compound produced the highest permeability value. It also  
29    produced membranes which had the most uniform morphology when  
30    examined in cross section under microscopic examination.

1           Samples of the membrane were soaked from coated cores and tested  
2       for tensile properties. A miniature dogbone shaped steel rule die was used to  
3       punch out samples for testing. The dogbone-shaped samples were pulled on  
4       tensile tester. The modulus of elasticity, elongation at break, and toughness  
5       values for the 70/30 cellulose acetate/Pluronic F68 membrane were high; 59  
6       kgf/mm<sup>2</sup>, 23%, and 0.3 kgf/mm<sup>2</sup>, respectively.

7           Therefore, this membrane which was formulated with a surfactant flux  
8       enhancer and sprayed from a single solvent had a high water permeability  
9       value, had good mechanical properties, and was reproducible.

10

11

TABLE 1

Surfactant Enhancer	Melting Point (°C)	Mol. Wt (g/mole)	Permeability (k x 10 <sup>4</sup> ) (cm.mil/atm.hr)
Myrj 52S	38	2,047	10.7
Myrj 53	42	2,487	13.2
Tween 20	<25	1,126	9.3
Tween 40	13	1,282	6.5
Tween 80	<25	1,309	6.2
Luviskol VA37E	67(T <sub>g</sub> )	45,000	2.2
Luviskol VA64P	106(T <sub>g</sub> )	44,000	7.1
Pluronic F68	52	8,600	15.4
Pluronic F108	57	14,600	12.3
Pluronic F127	56	12,600	10.5

12

13           In Table 1, Myrj® 52s denoted polyoxyethylenated stearic acid with 40  
14       moles of ethylene oxide; Myrj® 53 denotes polyoxyethylenated stearic acid  
15       with 50 moles of ethylene oxides; Tween® 20 denotes polyoxyethylenated  
16       sorbitan monolaurate with 20 moles of ethylene oxide; Tween® 40 denoted  
17       polyoxyethylenated sorbitan monopalmitate with 20 moles of ethylene oxide;  
18       Tween® 80 denotes polyoxyethylenated sorbitan monoleate and 20 moles of

1     ethylene oxide; Luviskol® VA 37E denotes vinylpyrrolidone/vinyl acetate  
2     copolymer with 30 wt % of vinylpyrrolidone and 70 wt % of vinylacetate;  
3     Luviskol® VA 64P denotes vinylpyrrolidone/vinyl acetate copolymer with 60 wt  
4     % vinylpyrrolidone and 40% vinyl acetate having a molecular weight of  
5     approximately 60,000; Pluronic® F68 denotes polyoxypropylene glycol of  
6     8,600 molecular weight and 160 moles of ethylene oxide; Pluronic® 108  
7     denotes polyoxypropylene glycol of 14,600 molecular weight and 280 moles  
8     of ethylene oxide; and Pluronic® 127 denotes polyoxypropylene glycol of  
9     12,600 molecular weight and 200 moles of ethylene oxide. The Myrij and  
10    Tween products are commercially available from the ICI Americas, Inc.,  
11    Wilmington, Delaware. The Pluronic and Luviskol products are available from  
12    BASF Corporation, Mt. Olive, New Jersey.

13           In as much as the foregoing specification comprises present  
14     embodiments of the invention, it is understood, variations and modifications  
15     can be made, in accordance with the disclosed invention, without departing  
16     from the scope of the invention.

1    We Claim:

2

3    1.    A composition comprising a polymer for providing a polymer  
4    membrane, at least one pharmaceutically acceptable surfactant compatible  
5    with the polymer, and a single solvent for both the polymer and the surfactant.

6

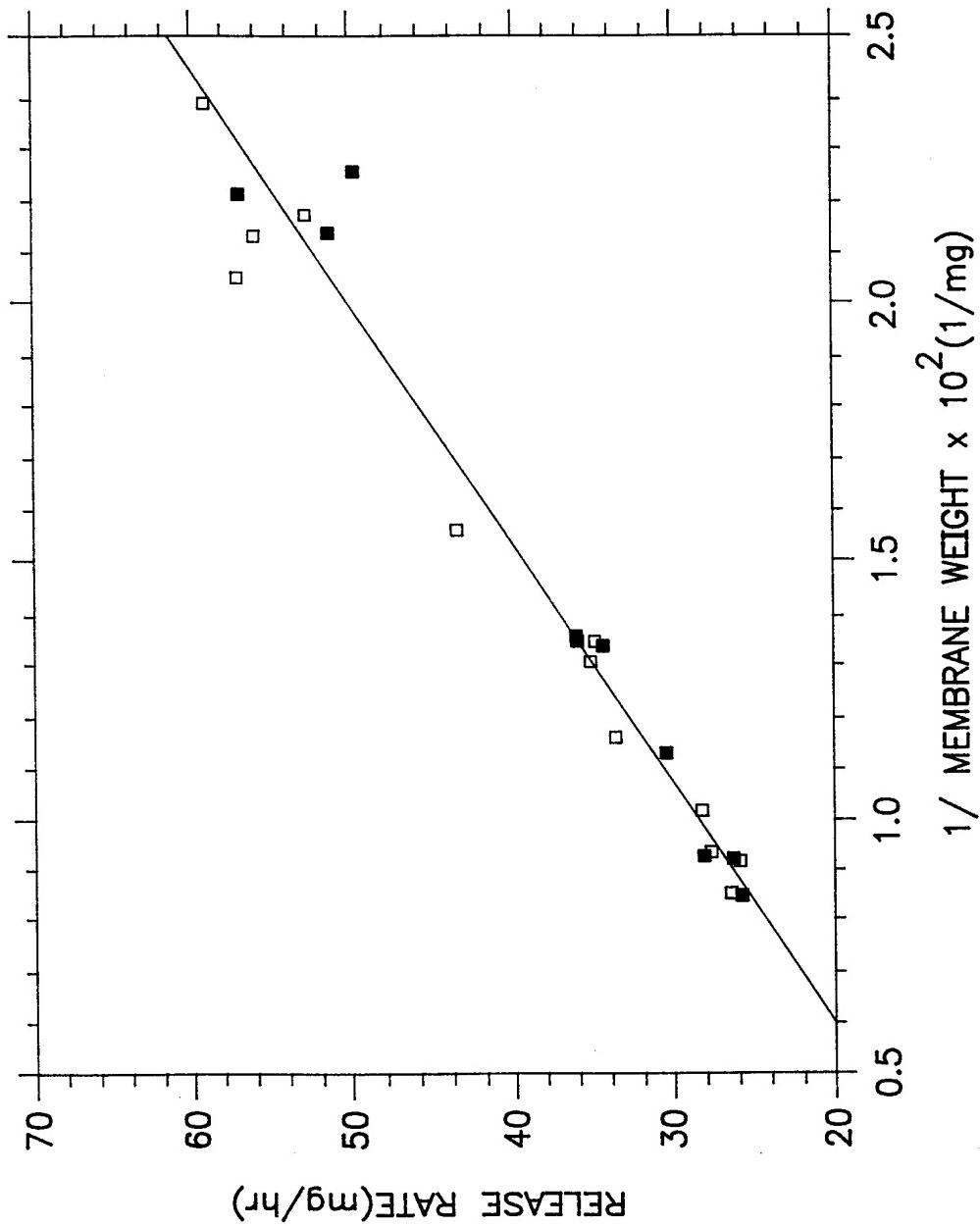
7    2.    A composition comprising 40 wt % to 99.5 wt % of a member selected  
8    from the group consisting of cellulose acylate, cellulose diacylate, cellulose  
9    triacylate and ethylcellulose; 0.5 wt % to 60 wt % of an amphiphilic surfactant,  
10   and an organic solvent wherein the cellulose member and the amphiphilic  
11   surfactant exhibiting a solubility.

12

13   3.    A composition comprising 40 wt % to 99.5 wt % of a member selected  
14   from the group consisting of a cellulose acetate, a cellulose diacetate, a  
15   cellulose triacetate, and ethyl cellulose; 0.5 wt % to 60 % of an amphiphilic  
16   surfactant; which composition when coated onto a therapeutic drug  
17   composition provides a dosage form for administering the drug over time.

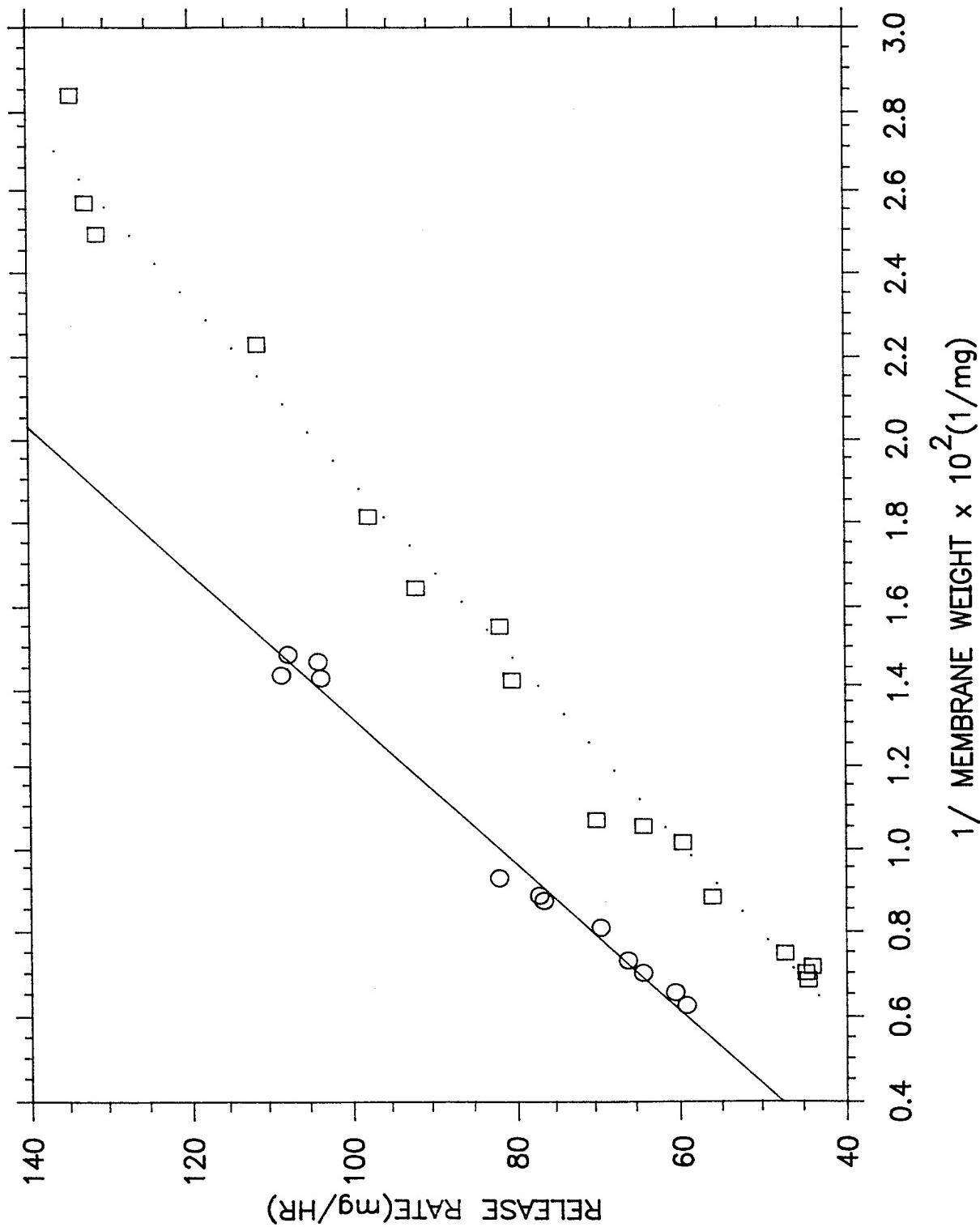
18

19   4.    A dosage form comprising: (1) a composition comprising a dose of  
20   drug; (2) a composition comprising a polymer and an amphiphilic surfactant  
21   that surrounds (1); and wherein the dosage form is characterized by : (3) a  
22   solvent exhibiting common solubility for the polymer and the surfactant for  
23   surrounding (1) with (2) to provide the dosage form.

**FIG. I**

2 / 4

FIG. 2



3 / 4

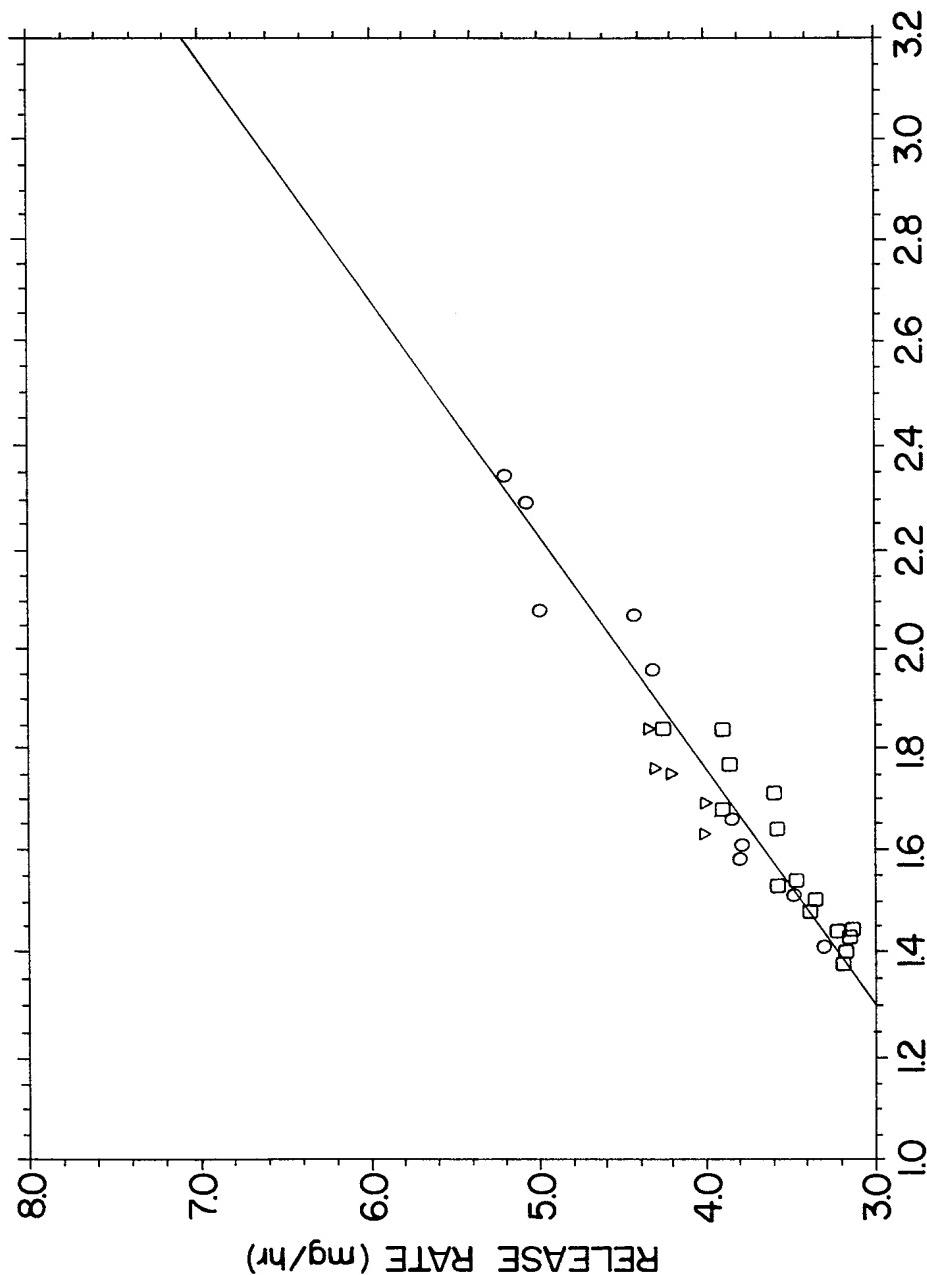
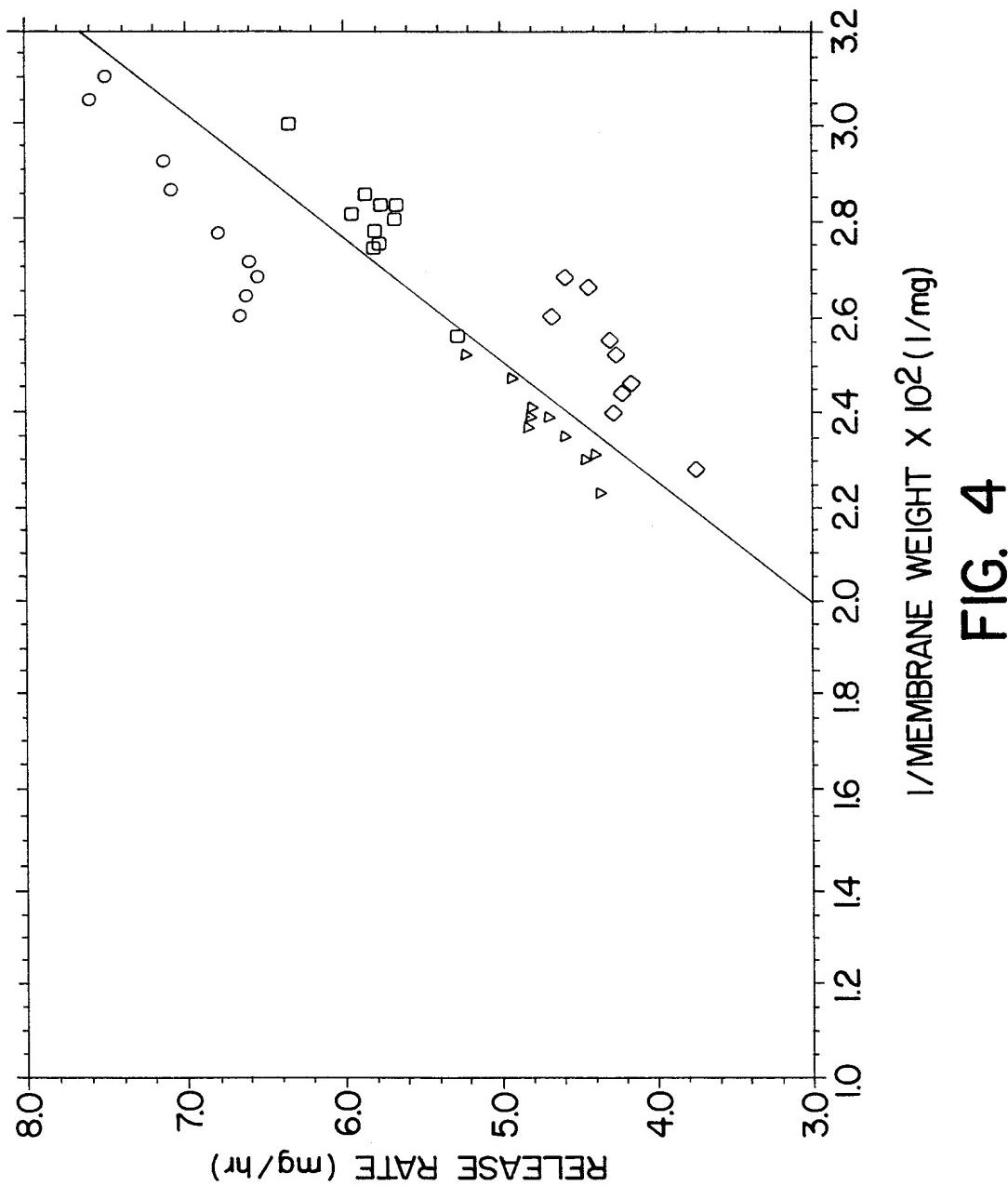


FIG. 3

4 / 4



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/18512

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 A61K9/28 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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A	EP 0 459 516 A (KIRIN AMGEN INC) 4 December 1991 ----	
A	EP 0 339 811 A (ALZA CORP) 2 November 1989 -----	



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Patent family members are listed in annex.

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